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Retinitis Pigmentosa in a Young Man With Noonan Syndrome: Further Evidence That Noonan Syndrome (NS) and the Cardio-Facio-Cutaneous Syndrome (CFC) Are Variable Manifestations of the Same Entity?

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We report on a young man with Noonan syndrome (NS) and retinitis pigmentosa. As far as we know, retinitis pigmentosa has not been reported in NS. However, in the 3 cardio-facio-cutaneous syndrome (CFC) patients in whom electroretinographic studies were performed, retinal anomalies have been found. In addition, decreased vision, refractive errors, strabismus, and optic disc anomalies were reported in CFC patients. This observation suggests that NS and CFC are variable manifestations of the same entity. © 1996 Wiley-Liss, Inc.

KEY WORDS: cardio-facio-cutaneous (CFC) syndrome, Noonan syndrome, retinitis pigmentosa, autosomal dominant inheritance

INTRODUCTION

The cardio-facio-cutaneous syndrome (CFC), as originally described by Reynolds et al. [1986], is characterized by a distinct Noonan-like facial appearance, heart and skin anomalies, short stature, delayed psychomotor development, and minor anomalies. In the original report, "eye abnormalities" were already listed as a clinical manifestation of the syndrome, but the eye findings were specified further only recently [Young et al., 1993].

The resemblance between CFC and the Noonan syndrome (NS) opened the debate as to whether or not both conditions are variable manifestations of the same entity. Fryer et al. [1991] reported on the evolution of the clinical phenotype in a patient with CFC and questioned the validity of separating CFC from NS. Conversely, Neri et al. [1991] reviewed the available clinical data on both conditions and concluded that "the Noonan and CFC syndromes are indeed distinct and separate conditions." They emphasized that one of the characteristic differences between these conditions is that CFC cases are always sporadic, whereas familial occurrence compatible with autosomal dominant transmission is frequent (30–75%) in NS.

CLINICAL REPORT

V.L., a boy, was born as the second child in a family with 3 children. The 2 sibs, a boy and a girl, and both parents are normal. At his birth, the mother was 28 and the father 32 years old. Family history is unremarkable with regard to congenital malformations, mental handicap, and consanguinity. Pregnancy and term delivery were normal. Birthweight was 3,100 g, length was 48 cm, and head circumference (OFC) was 36 cm. No perinatal problems were noted. Psychomotor development was retarded from the beginning: he sat without support at the age of 9 months and walked at 2 years. At 6 years, bilateral palpebral ptosis and strabismus were corrected. School results were satisfactory, with normal intelligence (IQT = 106, WISC-R). At the age of 8 years, V.L. underwent surgery for bilateral inguinal hernia and cryptorchidism. Serious behavioral problems with anorexia were noted after the unexpected death of his father, and he was admitted to the university hospital. Magnetic resonance imaging of the brain was normal except for a small cystic lesion, 1 cm in diameter, in the left temporal region. Further ophthalmological examination showed decreased visual acuity (5/10 o.u.) and astigmatism; electroretinography showed markedly reduced retinal responses that were most pronounced at the right eye and 30° constriction of the visual fields, consistent with the diagnosis of retinitis pigmentosa. Morphologic retinal changes were not present. He was enrolled in a school for the visually handicapped. Cardiac echography demonstrated discrete dilatation of the pulmonary artery, normal pulmonary, and aortic valves and no ventricular or atrial septal defects. Results of an X-ray skeletal survey, re-

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nal echography, and routine hematological and biochemical examinations were normal.

At 13 8/12 years old, V.L.'s psychosocial integration is normal without behavioral problems. His weight is 38 kg (25th centile for his age), his height is 143 cm (3rd centile is 148 cm), and his OFC is 53.5 cm (50th centile for his age). Craniofacial appearance is distinct (Fig. 1), with curly thin hair, ocular proptosis, discrete palpebral ptosis, and "coarse" facial features consisting of a flat nasal bridge, broad nasal tip, long philtrum, thick lips, relative maxillary hypoplasia, and high-arched palate. His neck is short and broad, with discrete webbing and low posterior hairline. The thorax is broad and short, with widely spaced nipples and a supernumerary, rudimentary nipple on the left. Genital development is normal with prepuberal testes. The skin is dry, with acrocyanosis of fingers and toes. Bone age as measured on an X-ray film of the left hand corresponds to his chronological age.

Chromosome analysis on a peripheral blood lymphocyte culture demonstrated a 46,XY normal male karyotype after G and R banding.

DISCUSSION

The concurrence of retinitis apparent pigmentosa in the present pubertal boy with Noonan phenotype is interesting in several aspects. The facial "Gestalt" and the additional clinical findings support the diagnosis of NS. However, as far as we know, retinitis pigmentosa has never been documented in patients with NS [Lee et al., 1981]. In addition to palpebral ptosis, proptosis, and strabismus, further ophthalmological examination in the boy showed markedly decreased vision with astigmatism and electroretinographic evidence of retinitis pigmentosa with 30° narrowing of visual fields.

Fig. 1. The typical NS craniofacial appearance.

An alternative diagnosis could be CFC as originally described by Reynolds et al. [1986].

Review of the literature produced ophthalmological findings on 32 patients with CFC: 15 females and 17 males with a mean age of 4 3/12 years (range = .5–13 1/2 years). In all these patients, the clinical findings were well described and are listed in Table I, including the data of the present patient. Hypertelorism (25/32), epicanthal folds (19/32), and palpebral ptosis (16/32) were present in at least half of the patients. Strabismus (15/32) and nystagmus (8/32) were other common findings, whereas cataracts (2/32), periocular hemangioma (2/32), and microcornea (1/32) were noted only in a few patients [Reynolds et al., 1986; Neri et al., 1987; Verloes et al., 1988; Chrzanowska et al., 1989; Mucklow, 1989; Sorge et al., 1989; Gross-Tsur et al., 1990; Matsuda et al., 1991; Adès et al., 1992; Ghezzi et al., 1992; Somer et al., 1992; Dunya et al., 1993; Raymond and Holmes, 1993; Young et al., 1993].

However, data on additional complete ophthalmological examinations are available in only 10 of these 32 patients, and visual acuity tests were performed in only 8. Optic disk abnormalities, i.e., segmental dysplasia (1 patient), "tilted" optic disk (1 patient), pale optic disks (2 patients), or a combination of both anomalies (1 patient) were noted in 5 of the 10 examined patients [Adès et al., 1992; Ghezzi et al., 1992; Dunya et al., 1993; Raymond and Holmes, 1993; Young et al., 1993]. Electroretinographic studies were only performed in 3 patients [Adès et al., 1992; Dunya et al., 1993; present patient] with abnormal results in all 3, i.e., poorly developed papillomacular bundles, retinal dystrophy, or retinitis pigmentosa. Decreased vision was noted in 6 of the 8 examined patients, with significant astigmatic refractive errors as the most frequent anomaly (5 patients) [Adès et al., 1992; Raymond and Holmes, 1993; Young et al., 1993; present patient].

Thus, the present observation supports the view of Fryer et al. [1991] that "patients with the CFC phenotype represent mutations at adjacent loci, i.e., CFC and NS may be examples of contiguous gene syndromes."

In addition, the ophthalmological findings in the present pubertal male with Noonan phenotype and our review on ophthalmological abnormalities in CFC indicate that ophtalmological abnormalities may be an inherent part of the syndrome. Ophthalmological investigations are to be recommended in patients with CFC and NS and should include periodical visual acuity tests, funduscopy, and electroretinography.

TABLE I. Clinical Ophthalmologic Findings in CFC: Literature Data on 31 Patients and Present Patient

Abnormalities	No. of patients	%
Hypertelorism	25/32	78.1
Epicanthal folds	19/32	59.4
Palpebral ptosis	16/32	50.0
Strabismus	15/32	46.8
Nystagmus	8/32	25.0
Cataract(s)	2/32	6.8
Periocular hemangioma	2/32	6.8
Microcornea	1/32	3.1

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